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The focus of the research is to understand the role that the widely-divergent, globally-acting locus coeruleus (LC)-noradrenergic (NA) system plays in sensory information processing. Completed light-microscopic studies of the regional and laminar distribution of cortical innervation by extrathalamic systems (e.g., noradrenergic, cholinergic, serotonergic, and dopaminergic) indicate that axons of each system exhibit a different density and laminar distribution. They also display individual developmental sequences in terms of the time innervation begins and the evolution of its specialized laminar distribution in each cortical region. These anatomic data support the proposal that each extrathalamic system contacts a distinct population of neurons in specific cortical regions. Each population of neurons may be involved in different aspects of cortical processing. Cellular electrophysiology studies suggest that activity in the LC-NA has specific modulatory effects on the sensory responsiveness of cortical neurons. Specifically, it alters the excitatory and inhibitory componenets of these sensory responses. Functionally, the LC-NA system may be involved

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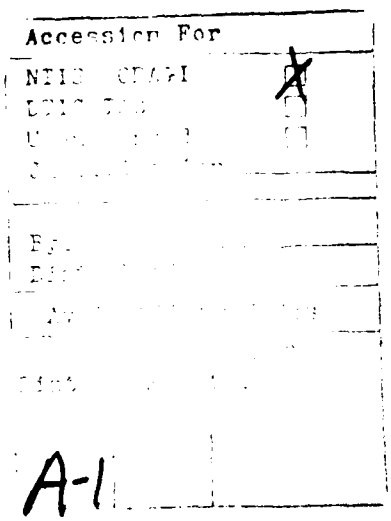
in the orienting and attentional mechanisms indexed by the surface-recorded P300, a slow wave that appears in response to novel and/or task-relevant events. Bilateral lesions of the nucleus LC result in decreased magnitude of this component.

Work currently underway will continue to define the spatial domain over which the system exerts its influence, the temporal domain during which it is active, and the functional domain in which particular behavioral consequences occur.



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Scientific Progress

The goal of these studies is to characterize the effects of the noradrenergic (NA)-locus coeruleus (LC) system on cortical information processing. Our scientific progress is described below in sections addressing the types of studies completed and currently underway.

I. **Monkey Event-Related Potentials (ERPs)**

A. **Completed Studies**

Visual ERPs. Studies conducted during Year-01 showed that an electrophysiological measure resembling the human P300 potential could be recorded in monkey using an appropriate "oddball" paradigm (Pineda et al., 1987; 1988). In humans, this electrical potential is believed to be related, among other things, to selective attention, context-updating, and encoding of memories. Lesion studies conducted during Year-02 suggested that NA-LC is critical for the genesis of monkey auditory P300 (Pineda et al., 1989). However, one defining property of human P300 is its modality non-specificity. That is, P300s generally display similar properties whether elicited by auditory, visual, or somatosensory stimuli (Squires et al., 1977). One explanation for these similarities is that multi-modal stimulation engages similar mechanisms. In the present study (Pineda et al., in preparation), visual ERPs (VEPs) were recorded from chronically implanted electrodes in seven squirrel monkeys (Saimiri sciureus). The results indicate that P300-like potentials are recorded in monkeys in a visual "oddball" paradigm. These potentials exhibit responsiveness to stimulus probability and to trial-to-trial changes in stimulus sequence, two properties which characterize the human P300. Studies involving lesions of the LC nucleus, which will address what role NA-LC plays in the genesis of visual P300, are currently underway.

Drug Studies. Pharmacologic activation or suppression of source-cell activity using drugs provides a more specific and reversible method of studying the relationship between LC activity and the variety of electrophysiological indices that measure cortical information processing. The role of NA-LC in the genesis of P300 was examined in the present study (Swick et al., in preparation) by recording event-related potentials (ERPs) in squirrel monkey (Saimiri sciureus) before and after systemic administrations of the alpha-2 adrenergic agonist, clonidine. Six chronically implanted monkeys, 2 trained and 4 untrained, were tested with 3 doses of clonidine

(0.05, 0.075, 0.1 mg/kg IM) in an auditory "oddball" paradigm (1 and 6 KHz tones, 200 msec duration, one second ISI). Two of the untrained subjects showed habituation in P300-like potentials during the course of the study, thus their data were difficult to interpret. The remaining subjects showed significant decreases in P300 amplitude following clonidine administration, particularly at the highest dose, while showing recovery in post-drug sessions.

These data suggest that NA-LC activity is specifically involved in the genesis of monkey P300 potentials elicited under passive (untrained) or active (trained) conditions.

Brainstem Auditory Evoked Potentials (BAEPS). Field potentials recorded on the scalp, following the rapid presentation of short-duration acoustic stimuli, reflect electrical activity in auditory nuclei and pathways in the brain stem. Initial observations reported in the literature suggest that each peak of the BAEP reflects the processing of acoustic signals in specific nuclei, such as the VIIIth nerve, cochlear nucleus, superior olivary complex, lateral lemniscus, inferior colliculus, medial geniculate, and thalamocortical radiation, respectively (Jewett, 1970; Picton et al., 1974; Huang and Buchwald, 1977). More recent observations argue that BAEP peaks reflect superposition of field potentials from multiple sources (Moller and Jannetta, 1982; Wada and Starr, 1983; Legatt et al., 1986). In the present study (Pineda et al., in press) BAEPs were recorded from chronically implanted epidural electrodes in ten squirrel monkeys (Saimiri sciureus). The effects of stimulus intensity, repetition rate, and anesthesia (Ketamine 20 mg/kg IM) on peak latencies and inter-peak intervals were evaluated. Monkey waveforms consisted of approximately seven peaks (I-VII). As with human, these peaks exhibited significant decreases in latency with increasing intensity (I-IV) and increases in latency with increases in repetition rate (III, V, and VI). Inter-peak intervals were similar to those observed in human. Furthermore, ketamine anesthesia significantly delayed the latencies of most peaks, except I, V, and VII.

Since previous studies have suggested that central transmission along auditory pathways may in part be modulated by extrathalamic afferents to cortex (Mendel, 1977; Bhargava et al., 1978; Savaki et al., 1978; Furlow et al., 1980), BAEPs provide us with an additional sensitive assay of activity to determine the site of action of noradrenergic effects, i.e., whether cortical or pre-cortical. Preliminary studies suggest that extensive lesions of the locus coeruleus nucleus affect BAEP peak latencies but not amplitudes (Pineda et al., 1988).

Augmenting-Reducing Event-Related Potentials (ERPs). Changes in the amplitude of some components of the ERP with increasing stimulus intensity are used to define two categories of human subjects: those who exhibit large amplitude increases ("augmenters") and those who exhibit small increases or decreases in amplitude ("reducers"). These categories show strong correlations with a number of personality indices and with certain neuropsychiatric conditions. Previous human and animal studies have suggested that these categories may reflect differences in the levels of catecholamine neurotransmitters. Comparable data from non-human primates, which would allow tests of these hypotheses, are limited. In this study (Pineda et al., submitted) auditory ERPs were recorded from chronically implanted epidural

electrodes in five squirrel monkeys (Saimiri sciureus) in response to tones (500 Hz, 300 msec duration) of varying intensity (50, 60, 70, 80 dB SPL). The data indicate similarities between human and monkey ERPs in the morphology and topography of ERP components recorded during the 200 msec interval following stimulus presentation. Typically, peak amplitudes at mid-cortical sites (i.e., Fz, Cz, Pz) increased substantially with increasing stimulus intensity. In contrast, only small increases or even decreases in amplitude were evident over lateral temporal sites (i.e., T3, T4). These site-specific response profiles also exhibited considerable temporal stability. These data indicate that human and monkey exhibit similar responses to changes in stimulus intensity and provide a model to investigate the role of noradrenaline in the "augmenting-reducing" phenomenon.

B. Ongoing Studies

Drug Studies. Two trained and 4 untrained monkeys have been tested in the auditory "oddball" paradigm with the specific alpha-2 adrenergic agonist, guanfacine. Guanfacine is reported to be a more specific alpha-2 antagonist than clonidine and to not have its sedative effects. This study addresses the issue of whether the reductions in P300 amplitude described above were due to these sedative effects of clonidine. Preliminary results have been variable, with some subjects exhibiting an enhancement of P300-like activity, others showing a reduction, and still others showing no change. A finding that may bear on these conflicting results is currently being studied in greater detail by examining the relationship between behavioral state, as measured by the EEG, and the ERP. Preliminary data suggest that P300 is enhanced by guanfacine if the EEG is desynchronized and not affected if the EEG is synchronized.

Depth ERP Recordings. The strategy of recording ERPs intracranially may be useful in addressing the question of whether P300-like activity is generated by a single or multiple source(s). It could also be useful in determining the extent of noradrenergic involvement in P300 generation at various cortical and subcortical sites. Two monkeys have been chronically implanted with twisted wire electrodes. These electrodes were oriented towards the hippocampus and specific cortical regions (e.g., cingulate, frontal, and parietal cortex). Subsequent histology revealed that hippocampal electrodes were located medial to the target area. Nonetheless, P300-like components, similar to those recorded at the scalp surface, were recorded from hippocampal and cingulate sites.

Operant Training. Long-latency ERPs elicited during the performance of operant tasks differ in many respects from those recorded when subjects passively receive sensory stimulation. Operant training in visual and auditory discrimination tasks is thus an ongoing project.

II. Effects of Locus Coeruleus (LC) Activation on Forebrain Electroencephalographic (EEG) Activity

We have utilized our previously developed recording/infusion probe to activate the neurons of the LC in halothane-anesthetized rats while simultaneously recording EEG activity in the frontal cortex and the hippocampus. This experiment has now been replicated in 15 animals, with the following findings: 1) LC activation is consistently followed, within 2 to 70

seconds, by cortical EEG desynchronization and hippocampal theta, 2) if the recording/infusion probe is located so that the infusion is not effective in activating LC neurons, no such forebrain effects are noted, 3) following infusion-induced activation, forebrain EEG returns to pre-infusion patterns with about the same time course as the recovery of LC activity (10-20 minutes for complete recovery). These studies are continuing, with additional control experiments being performed and the effects of LC inactivation being assessed.

These observations provide evidence that LC activity levels are not only correlated with measures of forebrain activation but can be causally related to cortical and hippocampal EEG patterns.